BlueCross BlueShield of Alabama

Name of Policy:
Benlysta® (Belimumab)

Policy #: 250
Category: Pharmacology

Latest Review Date: April 2011
Policy Grade: A

Background/Definitions:
As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts have such coverage.

The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:

1. *The technology must have final approval from the appropriate government regulatory bodies;*
2. *The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;*
3. *The technology must improve the net health outcome;*
4. *The technology must be as beneficial as any established alternatives;*
5. *The improvement must be attainable outside the investigational setting.*

Medical Necessity means that health care services (e.g., procedures, treatments, supplies, devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:

1. *In accordance with generally accepted standards of medical practice; and*
2. *Clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient's illness, injury or disease; and*
3. *Not primarily for the convenience of the patient, physician or other health care provider; and*
4. *Not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.*

Description of Procedure or Service:
Systemic lupus erythematosus (SLE), or lupus, is an autoimmune disease in which a person's immune system attacks various organs or cells of the body, causing damage and dysfunction. Lupus is called a multisystem disease because it can affect many different tissues and organs in

the body. Some patients with lupus have very mild disease, which can be treated with simple medications, whereas others can have serious, life-threatening complications. Lupus is more common in women than men, and for reasons that are not precisely understood, its peak incidence is after puberty. In the United States the prevalence of SLE is estimated to be about 53 per 100,000, translating to about 159,000 out of 300 million people in the US being affected.

Benlysta® is a B-lymphocyte stimulator (BLyS)-specific inhibitor approved by the FDA on March 9, 2011 for the treatment of adult patients with active, autoantibody-positive, systemic lupus erythematosus (SLE) who are receiving standard therapy, including corticosteroids, antimalarials, immunosuppressives and nonsteroidal anti-inflammatory drugs (NSAIDs). Benlysta® is administered as an intravenous infusion only, over a period of 1 hour and the recommended dosage regimen is 10mg/kg at 2-week intervals for the first 3 doses and at 4-week intervals thereafter.

Policy:

Benlysta® (belimumab) meets Blue Cross and Blue Shield of Alabama's medical criteria for coverage for the treatment of adult patients with active, autoantibody-positive, systemic lupus erythematosus (SLE) who are receiving standard therapy.

Benlysta® (belimumab) does not meet Blue Cross and Blue Shield of Alabama's medical criteria for coverage and is considered **investigational** for the following indications related to lupus or any other diseases:

- in patients with severe, active lupus nephritis; or
- in patients with severe, active central nervous system lupus; or
- in combination with other biologics; or
- in combination with intravenous cyclophosphamide

Blue Cross and Blue Shield of Alabama does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Cross and Blue Shield of Alabama administers benefits based on the members' contract and corporate medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

Key Points:

The safety and effectiveness of BENLYSTA were evaluated in three randomized, double-blind, placebo-controlled studies involving 2133 patients with SLE according to the American College of Rheumatology criteria (Trial 1, 2, and 3). Patients with severe active lupus nephritis and severe active CNS lupus were excluded. Patients were on a stable standard of care SLE treatment regimen comprising any of the following (alone or in combination): corticosteroids, antimalarials, NSAIDs, and immunosuppressives. Use of other biologics and intravenous cyclophosphamide were not permitted.

Trial 1: BENLYSTA 1 mg/kg, 4 mg/kg, 10 mg/kg
Trial 1 enrolled 449 patients and evaluated doses of 1, 4, and 10 mg/kg BENLYSTA plus standard of care compared with placebo plus standard of care over 52 weeks in patients with SLE. Patients had to have a SELENA-SLEDAI score of ≥ 4 at baseline and a history of autoantibodies (anti-nuclear antibody (ANA) and/or anti-double-stranded DNA (anti-dsDNA), but 28% of the population was autoantibody negative at baseline. The co-primary endpoints were percent change in SELENA-SLEDAI score at Week 24 and time to first flare over 52 weeks. No significant differences between any of the BENLYSTA groups and the placebo group were observed. Exploratory analysis of this study identified a subgroup of patients (72%), who were autoantibody positive, in whom BENLYSTA appeared to offer benefit. The results of this study informed the design of Trials 2 and 3 and led to the selection of a target population and indication that is limited to autoantibody-positive SLE patients.

Trials 2 and 3: BENLYSTA 1 mg/kg and 10 mg/kg
Trials 2 and 3 were randomized, double-blind, placebo-controlled trials in patients with SLE that were similar in design except duration - Trial 2 was 76 weeks duration and Trial 3 was 52 weeks duration. Eligible patients had active SLE disease, defined as a SELENA-SLEDAI score ≥6, and positive autoantibody test results at screening. Patients were excluded from the study if they had ever received treatment with a B-cell targeted agent or if they were currently receiving other biologic agents. Intravenous cyclophosphamide was not permitted within the previous 6 months or during study. Trial 2 was conducted primarily in North America and Europe. Trial 3 was conducted in South America, Eastern Europe, Asia, and Australia.

Baseline concomitant medications included corticosteroids (Trial 2: 76%, Trial 3: 96%), immunosuppressives (Trial 2: 56%, Trial 3: 42%; including azathioprine, methotrexate and mycophenolate), and antimalarials (Trial 2: 63%, Trial 3: 67%). Most patients (>70%) were receiving 2 or more classes of SLE medications.

In Trial 2 and Trial 3, more than 50% of patients had 3 or more active organ systems at baseline. The most common active organ systems at baseline based on SELENA SLEDAI were mucocutaneous (82% in both studies); immunology (Trial 2: 74%, Trial 3: 85%); and musculoskeletal (Trial 2: 73%, Trial 3: 59%). Less than 16% of patients had some degree of renal activity and less than 7% of patients had activity in the vascular, cardio-respiratory, or CNS systems.

At screening, patients were stratified by disease severity based on their SELENA-SLEDAI score (≤9 vs ≥10), proteinuria level (<2 g/24 hr vs ≥2 g/24 hr), and race (African or Indigenous-American descent vs. other), and then randomly assigned to receive BENLYSTA 1 mg/kg, BENLYSTA 10 mg/kg, or placebo in addition to standard of care. The patients were administered study medication intravenously over a 1-hour period on Days 0, 14, 28, and then every 28 days for 48 weeks in Trial 3 and for 72 weeks in Trial 2.

The primary efficacy endpoint was a composite endpoint (SLE Responder Index or SRI) that defined response as meeting each of the following criteria at Week 52 compared with baseline:

- ≥4-point reduction in the SELENA-SLEDAI score, and

- no new British Isles Lupus Assessment Group (BILAG) A organ domain score or 2 new BILAG B organ domain scores, and
- no worsening (<0.30-point increase) in Physician's Global Assessment (PGA) score.

The SRI uses the SELENA-SLEDAI score as an objective measure of reduction in global disease activity; the BILAG index to ensure no significant worsening in any specific organ system; and the PGA to ensure that improvements in disease activity are not accompanied by worsening of the patient's condition overall.

In both Trials 2 and 3, the proportion of SLE patients achieving an SRI response, as defined for the primary endpoint, was significantly higher in the BENLYSTA 10 mg/kg group than in the placebo group in both studies. The effect on the SRI was not consistently significantly different for the BENLYSTA 1mg/kg group relative to placebo in both trials. The 1 mg/kg dose is not recommended. The trends in comparisons between the treatment groups for the rates of response for the individual components of the endpoint were generally consistent with that of the SRI (Table 1). At Week 76 in Trial 2, the SRI response rate with BENLYSTA 10 mg/kg was not significantly different from that of placebo (39% and 32%, respectively).

Table 1. Clinical Response Rate in Patients with SLE After 52 Weeks of Treatment

Response[1]	Trial 2			Trial 3		
	Placebo + Standard of Care (n = 275)	BENLYSTA 1 mg/kg + Standard of Care[2] (n = 271)	BENLYSTA 10 mg/kg + Standard of Care (n = 273)	Placebo + Standard of Care (n = 287)	BENLYSTA 1 mg/kg + Standard of Care[2] (n = 288)	BENLYSTA 10 mg/kg + Standard of Care (n = 290)
SLE Responder Index	34%	41% (p = 0.104)	43% (p = 0.021)	44%	51% (p = 0.013)	58% (p < 0.001)
Odds Ratio (95% CI) vs. placebo		1.3 (0.9, 1.9)	1.5 (1.1, 2.2)		1.6 (1.1, 2.2)	1.8 (1.3, 2.6)
Components of SLE Responder Index						
Percent of patients with reduction in SELENA-SLEDAI ≥4	36%	43%	47%	46%	53%	58%
Percent of patients with no worsening by BILAG index	65%	75%	69%	73%	79%	81%
Percent of patients with no worsening by PGA	63%	73%	69%	69%	79%	80%

[1] Patients dropping out of the study early or experiencing certain increases in background medication were considered as failures in these analyses. In both studies, a higher proportion of placebo patients were considered as failures for this reason as compared to the BENLYSTA groups.

[2] The 1 mg/kg dose is not recommended.

The reduction in disease activity seen in the SRI was related primarily to improvement in the most commonly involved organ systems namely, mucocutaneous, musculoskeletal, and immunology

Key Words:
Benlysta®, belimumab, systemic lupus erythematosus, SLE

Approved by Governing Bodies:
Benlysta® was FDA approved March 9, 2011 to treat patients with active, autoantibody-positive, systemic lupus erythematosus (SLE) who are receiving standard therapy, including corticosteroids, antimalarials, immunosuppressives and nonsteroidal anti-inflammatory drugs (NSAIDs).

Benefit Application:
Coverage is subject to member's specific benefits. Group specific policy will supersede this policy when applicable.

ITS: Home Policy provisions apply.
AT&T contracts: No special consideration.
FEP: Special benefit consideration may apply. Refer to member's benefit plan. FEP does not consider investigational if FDA approved. Will be reviewed for medical necessity.
Wal-Mart: Special benefit consideration may apply. Refer to member's benefit plan.
Pre-certification requirements: Not applicable.
Pre-determination requirements: Pre-determinations will be performed as a courtesy review at the request of the physician and/or subscriber.

Coding:
HCPCS Codes:

Effective for dates of service on or after January 1, 2012:

J0490	Injection, Belimumab, 10mg

Effective for date of service July 1, 2011 through December 31,2011:

Q2044	Injection, Belimumab, 10mg

Effective for dates of service through June 30, 2011:

J3590	Unclassified biologics

References:

1. Benlysta® (belimumab), Full U.S. Prescribing Information and Medication Guide, http://www.benlysta.com.

Policy History:

Medical Policy Group, April 2011 **(1)**
Medical Policy Administration Committee, April 2011
Available for comment April 13 – May 30, 2011
Medical Policy Group, December 2011 **(1)** Update to Coding with new 2012 code J0490
